REMARKS

Claims 30-34 and 46-49 are pending. Claim 32 has been withdrawn as being drawn to a non-elected species. Applicants, however, are entitled to the consideration of claims to additional species in the event a generic claim is allowed. Claims 30 and 46 have been amended. The amendment of the claims in no way changes their scope. Support for the claim amendments can be found on page 17 of the specification and in the claims as originally filed. No new matter has been added.

Claim Objections

Claims 30, 46 and 49 have been objected to by the Examiner as being confusing and unclear due to the presence of two colons in independent claims 30 and 46. Although Applicants do not agree that the colons compromise the clarity of the claims, Applicants have amended the claims as suggested by the Examiner in order to expedite the prosecution of the present application.

Based on the amendment of claims 30 and 46 and the dependency of claim 49 from independent claim 46, Applicants respectfully request that the Examiner remove his objection to these claims.

Claim Rejections – 35 USC § 112

Claims 30, 31, 33, 34 and 46-49 have been rejected under 35 USC § 112, second paragraph "...as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Independent claims 30 and 46 are rejected for being indefinite for reciting a "modified product profile, wherein the modified product profile of the modified heparinase II is at least 10% different than a native product profile of a native heparinase II" and for the recitation of a "native product profile of a native heparinase II". It is argued that the specification does not provide a definition of what a native product profile is or how one can determine or what a product profile that is 10% different than a native product profile is.

Applicants respectfully traverse the Examiner's rejection. It is clear from the common language of the terms as well as the teachings of the specification (see the description of the sequences of heparinase I and II on page 11, lines 17-24 as well as the description of "modified

product profile" and how it relates to the product profile of the native enzyme on pages 20, line 25 through page 21, lines 3 and 23-25) that a native product profile of a native heparinase II is simply the set of enzymatic products of a reaction with native heparinase II on a substrate of the enzyme (i.e. a heparin-like glycosaminoglycan or a heparan sulfate-like glycosaminoglycan). The use of the term "native" merely distinguishes the heparinase II from the modified molecules of the present claims and is intended to refer to the protein that is not modified or is as it would be present in nature. Native, in this instance, imparts no other meaning than what is accepted as common usage of the word. Therefore, a product profile of a heparinase II molecule would be considered a native product profile so long as the heparinase II molecule used in the enzymatic reaction is as it would be if derived from a natural source (e.g., derived from *F. heparinum*). Applicants maintain that the plain language of the claims is sufficiently clear to allow one of ordinary skill in the art to know what a native product profile of a native heparinase II molecule is.

Regarding the argument on the variability in the choice of substrate and reaction conditions, Applicants respectfully disagree that this variability results in indefiniteness. Applicants maintain, as would be recognized by one of ordinary skill in the art, that modified heparinase II enzymes for use in the claimed methods are intended to include any modified heparinase II enzyme that has a modified product profile that is at least 10% different from the native heparinase II for any substrate these enzymes can act upon. As taught in the instant specification the substrates clearly include heparin-like glycosaminoglycans and heparan sulfate-like glycosaminoglycans. The properties and structures of which would be readily apparent to one of ordinary skill in the art. Applicants further maintain that one of ordinary skill in the art would recognize that the reaction conditions that may be used are any such that the degradation of the chosen substrate by the modified and native heparinase II molecules can be compared. The fact that there is a range of enzymatic conditions at which the degradative activity of an enzyme can be assessed is well-known and fully recognized in the art when conducting enzymatic assays; encompassing such a range does <u>not</u> impart indefiniteness to the claim. The claims are intended to encompass modified heparinase II molecules with modified product profiles that are at least 10% different from native heparinase II using any set of enzymatic conditions at which the product profiles can be assessed. Additionally, the specification on page 21, lines 23-30 and 21, lines 23-25 clearly provides that enzymatic assays can be performed in a

variety of manners and also specifically provides that the comparison of the native product profile and the modified product profile must be performed on the same substrate under identical conditions for the comparison of the product profiles to be appropriately made. The specification further provides examples of such an enzymatic reaction (on page 21 as well as Example 1). However, even without such an example, Applicants maintain that it would be clear to one of skill in the art that any appropriate set of conditions that would allow for the analysis of the degradation products between enzymes is encompassed by the rejected claims. As this would be clear to, and wholly expected by, one of ordinary skill in the art, Applicants maintain the claims are sufficiently definite.

Applicants also maintain that one of ordinary skill in the art would also know, based on the present specification as well as the general knowledge in the relevant art, how a product profile that is 10% different would be determined. As pointed out by the Examiner what is intended by the term "modified product profile" is described on page 20, lines 21-32. Applicants further maintain that it is sufficiently clear how one of ordinary skill in the art would be able to determine when a modified product profile is 10% different than a native product profile as recited in the present claims. As argued above it is clear that the native product profile of a native heparinase II molecule is the result of an enzymatic reaction of the native enzyme on a chosen substrate under a set of conditions. It is also clear that, for comparison, the modified product profile thus is the result of an enzymatic reaction of the modified heparinase II molecules on the same substrate under the identical set of conditions. As described on page 20, line 28 through page 21, line 3, the difference in the product profiles can be assessed according to the difference in the number of types of enzymatic products, the difference in the amount of a particular type of enzymatic product or simply the difference in the amount of enzymatic products *in toto* produced by the enzymes. It would be readily apparent to one of ordinary skill in the art that the results of the enzymatic reactions can be given in quantitative form and the presence of a 10% difference between the values of the native and modified heparinase II product profiles can be easily assessed. In addition to what would be apparent to one of ordinary skill in the art, the specification provides several methods that can be used to assess the product profiles of the enzymes of the claims. Pages 21 and 22 provide a method of assessing the product profiles through the use of MALDI-MS in combination with capillary electrophoresis (CE). Page 22 further provides other methods that can be used to assess the product profiles of

the enzymes and include methods that rely on viscosity, UV absorbance or mass spectrometry or CE alone. Therefore, based on the knowledge in the art and the description provided in the specification, one of ordinary skill in the art would know what a modified product profile of a modified heparinase II that is 10% different than a native product profile of a native heparinase II is.

Finally, the Examiner also maintains that it is unclear what is encompassed by the term "modified heparinase". Applicants respectfully maintain that this term is not unclear. The modified heparinase of the pending claims is clearly a modified heparinase II. It is further clear that the modified heparinase II is a heparinase II molecule that has the amino acid sequence of the mature peptide of SEQ ID NO: 2, optionally having conservative substitutions therein, which contains at least one amino acid residue that has been substituted with a different amino acid. The residues that may be substituted are clearly provided in the claims and are as follows: (a) a cysteine residue corresponding to position 348; (b) a histidine residue corresponding to at least one of positions 238, 252, 347, 440, 451, and 579; and (c) a heparin-binding sequence residue corresponding to at least one of positions 446-451. One of ordinary skill in the art would know that a modified heparinase II is a molecule that has the amino acid sequence of the mature peptide of SEQ ID NO: 2, which contains at least one of the amino acid substitutions provided above therein. One of ordinary skill in the art would further not confuse other heparinase enzymes for the modified heparinase II molecules of the claims. Heparinase I and III are completely different proteins with amino acid sequences different than the sequence of heparinase II. Additionally, following the recited definition of the modified heparinase II of the claims, it is sufficiently clear that modified heparinase II molecules cannot encompass heparinase I or III. Therefore, the Applicants assert that it is not unclear as to what a heparinase II is or what altered molecules are encompassed by the claims as the native sequence of heparinase II is provided (SEQ ID NO: 2) and the changes that may be made thereto are also provided. Applicants assert that it is not unclear that a modified heparinase II would not become a different modified heparinase molecule (e.g. heparinase I or heparinase III) as this is not possible due to the absence of recited modifications that could alter the native sequence of heparinase II in such a way.

Based on the foregoing arguments, the Examiner is respectfully requested to withdraw the rejection of claims 30, 31, 33, 34 and 46-49 under 35 USC § 112, second paragraph for indefiniteness.

Claim Rejections – 35 USC § 112

Claims 30, 33, 34 , 46, 47 and 48 are rejected under 35 USC § 112, first paragraph as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." It is argued that the identification of the amino acid residues important in the catalytic and binding activity of heparinase II as well as the limited number of described species is insufficient to demonstrate that Applicants were in possession of the invention as claimed.

Applicants maintain that the modified heparinase enzymes of the claims are limited to modified heparinase II enzymes with at least one substitution, wherein at least one substitution is selected from the residues as recited above. These modified heparinase II enzymes, as previously argued, do not include any modified heparinase molecules as asserted by the Examiner (modified heparinase I or III) but rather modified heparinase II molecules only. Applicants maintain that the structural limitations that are recited in the claims clearly indicate this and also clearly indicate that Applicants were indeed in possession of the claimed invention. The teaching of the native heparinase II sequence (SEQ ID NO: 2), description of the catalytic and binding sites of heparinase II, recitation of the possible amino acid substitutions, definition of conservative substitutions (page 17, line 24 through page 18, line 4) and no fewer than 17 examples of modified heparinase II molecules created and tested by the Applicants (see Examples 4 and 21) clearly are sufficient to signify to one of ordinary skill in the art that they were in possession of modified heparinase II molecules, namely a modified heparinase II that has the amino acid sequence of the mature peptide of SEQ ID NO: 2, which contains at least one amino acid residue that has been substituted with a different amino acid. The residues that may be substituted are, as clearly provided in the claims as follows: (a) a cysteine residue corresponding to position 348; (b) a histidine residue corresponding to at least one of positions 238, 252, 347, 440, 451, and 579; and (c) a heparin-binding sequence residue corresponding to at least one of positions 446-451. Furthermore, one of ordinary skill in the art will also recognize

that Applicants were in possession of modified heparinase II molecules which include further conservative substitutions as defined in the specification and known to those of skill in the art as well as non-conservative substitutions remote from the important catalytic and binding sites taught by the Applicants.

The relationship of these structural requirements (see above) with the functional limitations (e.g., pages 18-21 and Examples, especially 4 and 21) of the modified heparinase II molecules of the claims are clearly described in Applicants' specification. The recitation of the important catalytic and binding sites necessarily imparts that Applicants were indeed in possession of the genus of modified heparinase II molecules as recited above, which includes modified heparinase II molecules highly expected to exhibit altered function. Furthermore, Applicants description of the desired function of the modified heparinase II molecules along with the important active and binding sites is sufficient to signify possession to one of ordinary skill in the art the functional subset of the genus of modified heparinase II molecules described above. Additionally, although examples are not required, Applicants present several such modified heparinase II molecules, which exhibited altered activity as described in the rejected claims. Modified heparinase II molecules with substitutions at Cys 348, His 451, His 238, His 440 and His 579 are some of said examples. Applicants, therefore, stress that as the structure of the modified heparinase II molecules as well as the relationship to function are clearly presented, one of ordinary skill in the art would have no reason to doubt that Applicants were in possession of the modified heparinase II molecules as claimed.

The Examiner has further rejected the above claims as not being sufficiently enabled so that one of ordinary skill in the art would be able to make and use the claimed invention. The Examiner argues that although methods of producing variants are well-known in the art, sufficient guidance has not been provided to produce the variants with the claimed functional and structural limitations. The Examiner concludes that the specification does not provide guidance for one of ordinary skill to select from the infinite number of variants those that have the claimed properties; therefore, undue experimentation is required. The Examiner again also states that it is the combination of all modified heparinase variants with the corresponding substitutions in combination with the functional limitations that results in the enablement rejection.

Applicants assert that one of ordinary skill in the art is sufficiently enabled to make the modified heparinase II molecules of the claims, to test the modified heparinase II molecules for

the desired functional activity and to use the modified heparinase II molecules in the desired methods. The Examiner has conceded that methods of producing variants are well-known in the art. Applicants maintain that this is certainly true and that modified heparinase II molecules as defined above would be easily made with these well-known methods. Once a modified heparinase II molecule is made, Applicants assert that the experimentation needed to test these modified heparinase II molecules is no more than what is known and routinely expected in the art. Additionally, the specification provides adequate guidance by providing a number of methods that can be used to screen the modified heparinase II molecules for the desired function. As argued previously, examples of techniques for determining modified product profiles and/or k_{cat} values are given in the specification (e.g., pages 18, 21 and 22). Specifically, an enzymatic activity assay for determining the k_{cat} value of a heparinase enzyme and a method of using mass spectrometry and capillary electrophoresis for determining the product profile are described. Other methods provided (for determining product profiles) rely on viscosity, total UV absorbance or mass spectrometry or capillary electrophoresis alone. In view of this, one of skill would be required to perform only routine experimentation to screen the modified heparinase II molecules having the functions recited in the claims. Although the Examiner maintains that one of ordinary skill in the art would be reduced to making and testing all of the infinite possibilities of modified heparinase molecules, Applicants respectfully disagree. It is clear that the claim encompasses not any and all modified heparinases but modified heparinase II molecules. It is also clear that based on the definition of the modified heparinase II molecules of the claims, the number of possible mutants is far from infinite. The Examiner is respectfully reminded that according to the definition of modified heparinase II molecules of the claims the modified heparinase II molecules must have the amino acid sequence of the mature peptide of SEQ ID NO: 2 or having conservative substitutions therein, which has at least one amino acid substitution limited to the list of residues that may be substituted in (a)-(c) of claims 30 and 46. Additionally, Applicants further assert that it is Applicants teachings of the important active and binding sites that enable one of ordinary skill in the art to make modified heparinase II molecules with the altered function recited in the claims. Applicants maintain that it is routine in the art for those of ordinary skill to make mutants based on this information and to screen the mutants for the desired function. Applicants, therefore, conclude that with the high level of skill and knowledge in the art as well as the guidance provided in the specification one of ordinary skill in

the art is adequately enabled to make and use the invention commensurate in scope with these claims.

Based on the foregoing arguments, withdrawal of the rejection of claims 30, 33, 34 , 46, 47 and 48 under 35 USC § 112, first paragraph is respectfully requested.

Claim Rejections – 35 USC § 102

Claims 30, 33, 46 and 47 are rejected under 35 USC § 102(e) as being anticipated by Su et al. (US Patent No. 5,681,733). The Examiner maintains that as it is unclear as to what is encompassed by the term "modified heparinase", the teaching of heparinase III, which does not have a cysteine at position 348 of SEQ ID NO: 2, is encompassed by the modified heparinase II molecules of the claims. Therefore, the methods taught in Su et al. anticipate the rejected claims.

As argued above, Applicants maintain that the modified heparinase II molecules of the claims do not encompass heparinase III. The structure of the modified heparinase II molecules recited in the claims is such that the modified heparinase II has the amino acid sequence of the mature peptide of SEQ ID NO: 2, wherein at least one amino acid residue is substituted selected from a clearly defined list. Substitutions may also include those that are conservative in nature. This structural of definition of modified heparinase II molecules in no way embraces heparinase III as asserted by the Examiner.

Therefore, withdrawal of the rejection of claims 30, 33, 46 and 47 under 35 USC § 102(e) as being anticipated by Su et al. is respectfully requested.

Claim Rejections – 35 USC § 103

Claims 34 and 48 are rejected under 35 USC § 103 as being anticipated by Su et al. (US Patent No. 5,681,733) in view of Langer et al. (US Patent No. 4,373,023). The Examiner maintains that as it is unclear as to what is encompassed by the term "modified heparinase", the teaching of heparinase III, which does not have a cysteine at position 348 of SEQ ID NO: 2 is encompassed by the modified heparinase II molecules of the claims. The Examiner has also argued previously that Langer teaches neutralizing heparin in the blood with immobilized heparinase. Therefore, the Examiner concludes that the combination of Su et al. and Langer et al. render obvious the rejected claims.

Based on the above arguments, the Applicants again maintain that heparinase III is not encompassed by the definition of modified heparinase II molecules as recited in the claims. Therefore, the claims are not obvious based on the combination of Su et al. and Langer et al.

Applicants respectfully request the Examiner withdraw his rejection to the claims 34 and 48 under 35 USC § 103.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicants' representative at the telephone number listed below.

If the Examiner has any questions and believes that a telephone conference with Applicants' representative would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (extension 261).

Respectfully submitted,
Sasisekharan et al., Applicants

By: _____

Janice A. Vatland, Ph.D., Reg. No. 52,318
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone: (617) 720-3500

Docket No. M0656.70046US00
Date: August 25, 2003
x08/25/03x